Ethical Conflicts in Randomized Controlled Trials

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Outline

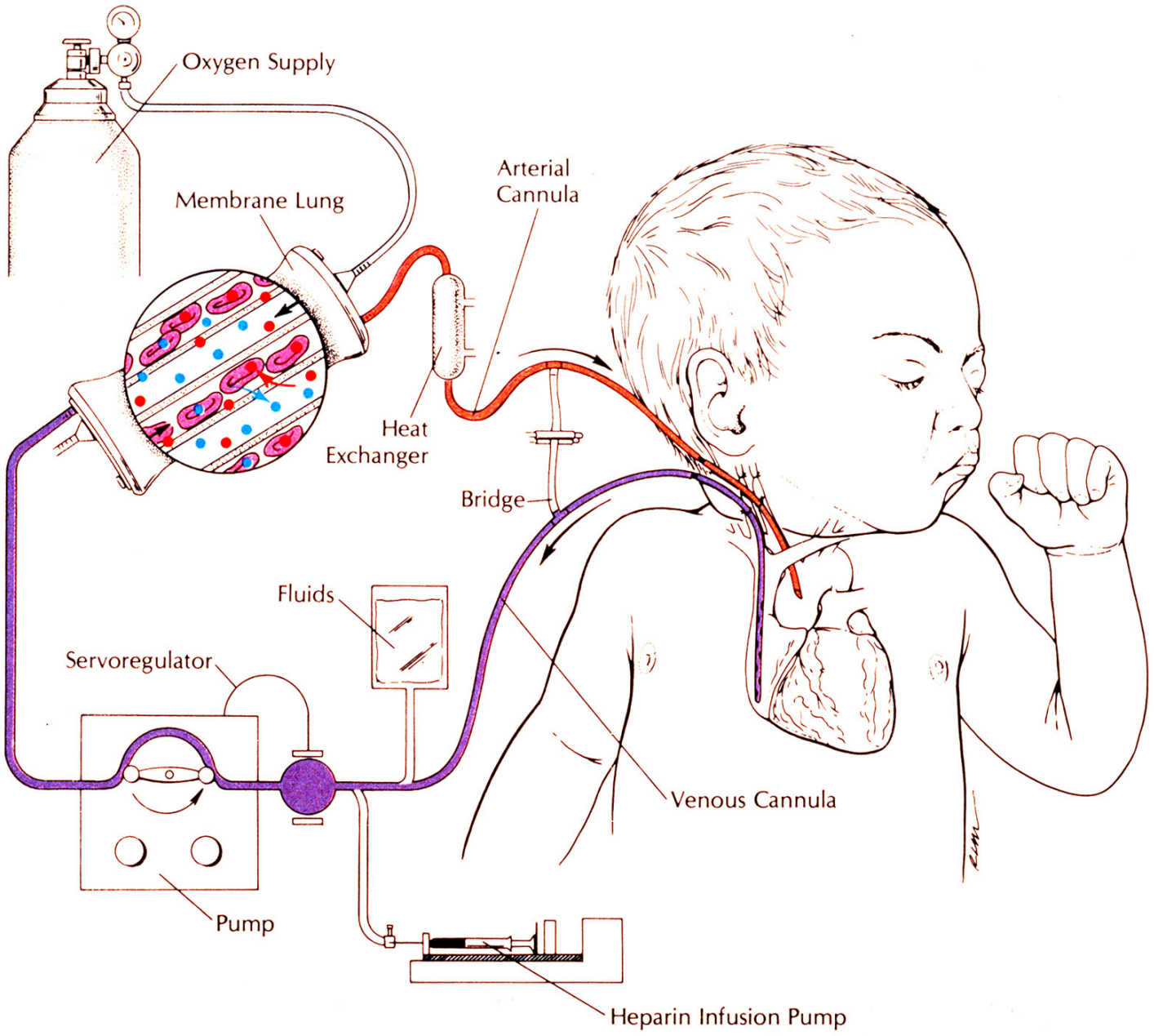
- ExtraCorporeal Membrane Oxygenation: *A Case Study*
- Clinician vs Investigator: *The Fundamental Conflict*
- Adaptive Randomization: *Balancing Conflicting Obligations*
- Randomized Consent: *Easing the Psychological Burdens*
- Are RCTs the only way to learn? *Ethical boundaries vs statistical certainty*

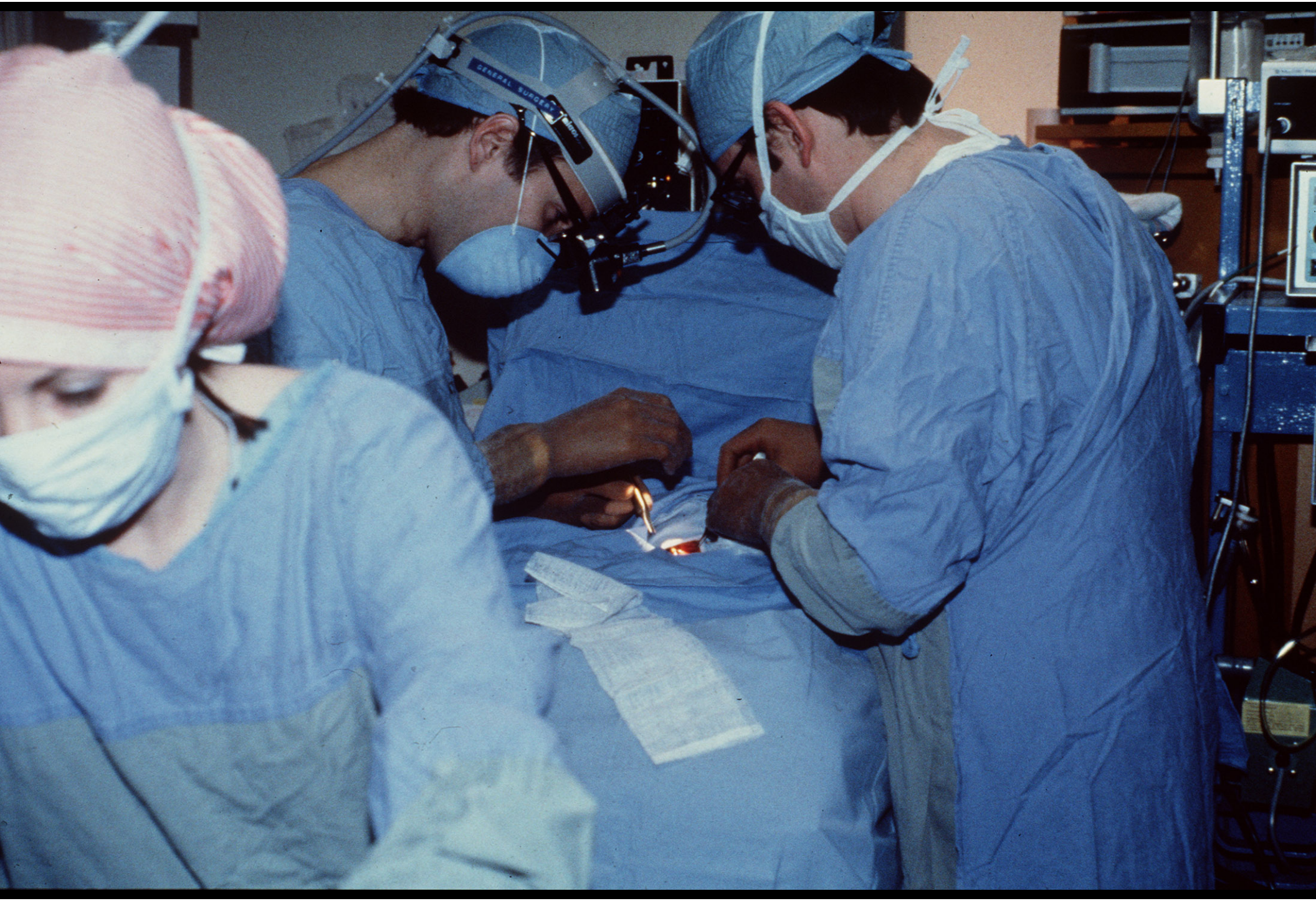
The Harvard Neonatal ECMO Trial

O'Rourke PP, Crone RK, Vacanti JP, Ware JH, Lillehei CW.

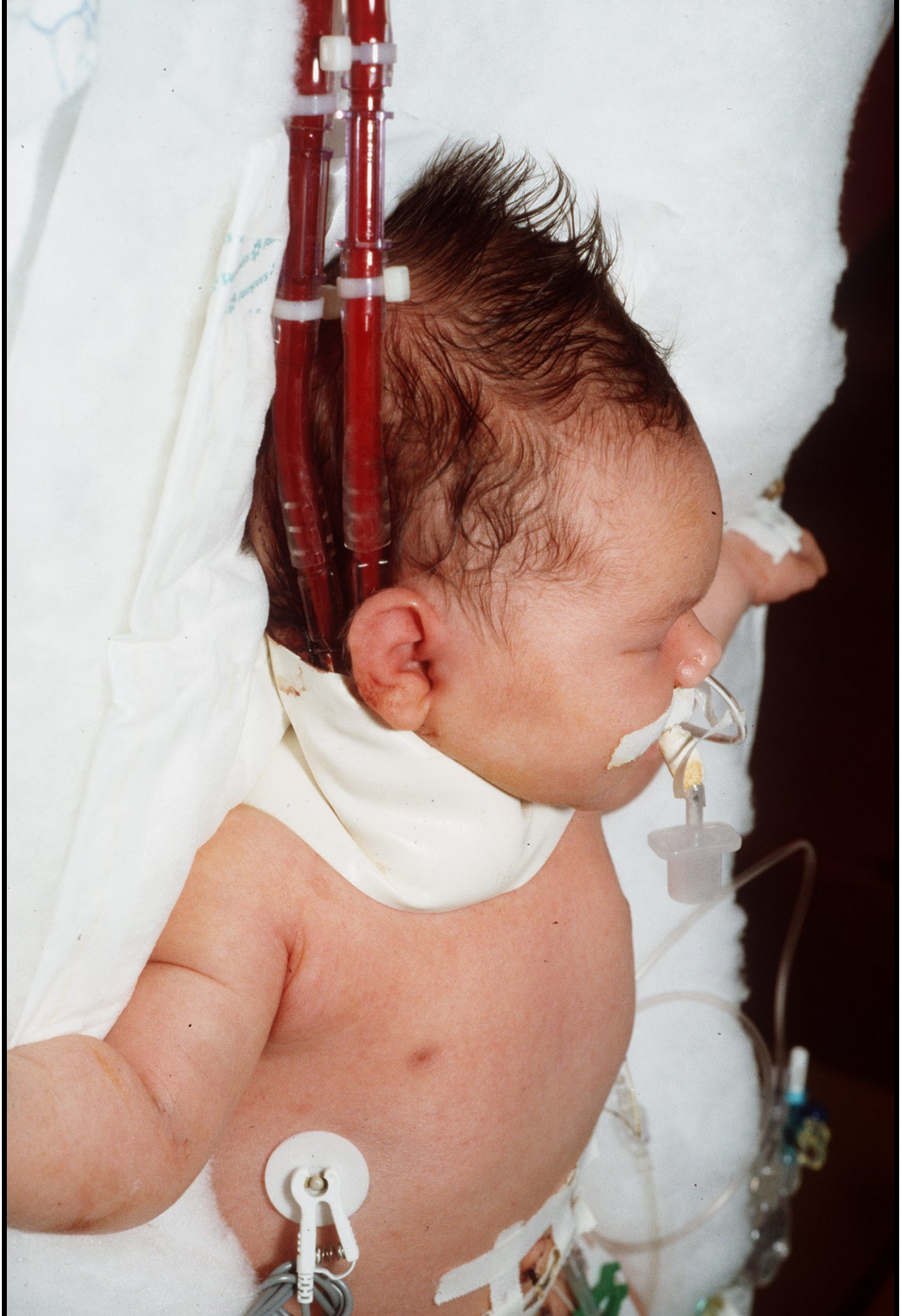
Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: a prospective randomized study.

Pediatrics 1989; 84:957-963.


Oxygen Supply
Membrane Lung
Arterial Cannula
Heat Exchanger
Bridge
Fluids
Servoregulator
Venous Cannula
Pump
Heparin Infusion Pump


GENERAL SURGERY


TO COME OFF E.C.M.O.
A. CLAMP VENOUS LINE.
B. UNCLAMP BRIDGE.
C. CLAMP ARTERIAL LINE.
D. DISCONNECT OXYGEN TUBING
FROM TOP OF MEMBRANE.
CURITY
CURITY



The Harvard Neonatal ECMO Trial

- Illustrates the deep conflict between the roles of clinician and investigator
- Utilized two unconventional techniques:
  - **Adaptive Randomization**
  - **Randomized Consent**
- Demonstrates our (sometimes irrational?) commitment to RCTs

Background to the Harvard Trial

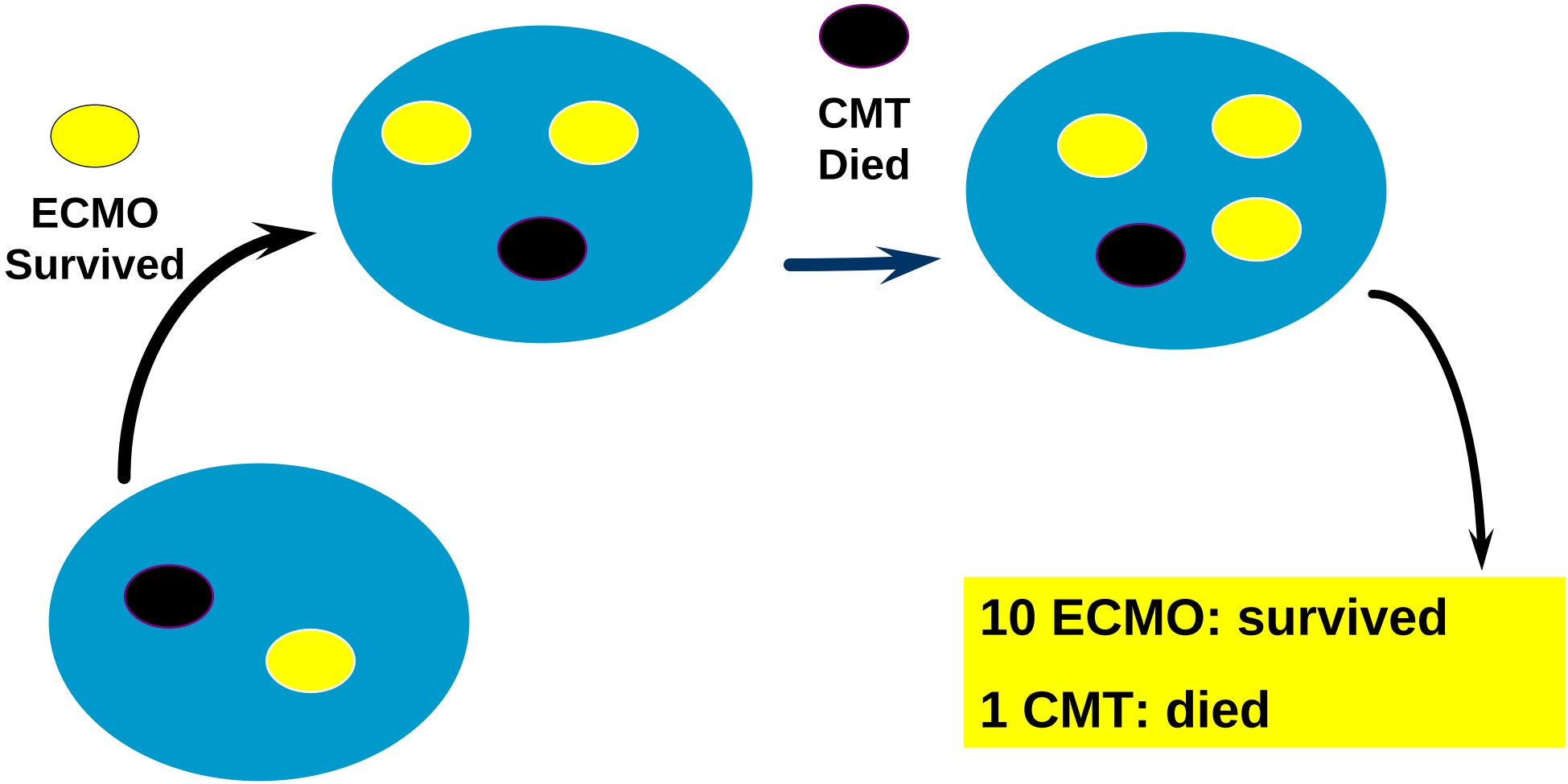
- An RCT in the 1970s had shown ECMO not effective for ARDS in adults
- In the 1980s, Robert Bartlett used ECMO to treat newborns with PPHN
- Results were very impressive
- But, pediatricians were reluctant to adopt ECMO without convincing data from an RCT

Pediatrics

Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study

Robert H. Bartlett, MD, Dietrich W. Roloff, MD, Richard G. Cornell, PhD, Alice French Andrews, MD, Peter W. Dillon, MD, and Joseph B. Zwischenberger, MD

Bartlett: Play-the-Winner Design



Extracorporeal Membrane Oxygenation and Conventional Medical Therapy in Neonates With Persistent Pulmonary Hypertension of the Newborn: A Prospective Randomized Study

P. Pearl O'Rourke, MD, Robert K. Crone, MD, Joseph P. Vacanti, MD, James H. Ware, PhD, Craig W. Lillehei, MD, Richard B. Parad, MD, and Michael F. Epstein, MD

From the Departments of Anesthesia, Surgery, and Newborn Medicine of the Children's Hospital, Harvard Medical School, and the Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts

The Harvard Neonatal ECMO Trial

Randomized newborns with PPHN to conventional therapy versus ECMO

Conventional Therapy

NICU: 7th Floor

Neonatologists

No patients had ever been offered ECMO

Anti-ECMO

ECMO

PICU: 5th Floor

Anesthesiologists & Surgeons

Already had experience with ECMO for newborns with CDH

Pro-ECMO

The Harvard Neonatal ECMO Trial:Study Design

- Eligible newborns had PPHN and a predicted mortality of 85% based upon retrospective data
- Phase I: 50/50 randomization until 4 deaths in one arm
- Phase II: Assign all pts to the more successful therapy, until 4 deaths in that arm or until statistical significance achieved
- Seek consent only from those randomized to the experimental therapy (ECMO)

The Harvard Neonatal ECMO Trial: Results

	ECMO	CMT
Phase I	**9 s, 0 d**	**6 s, 4 d**
Phase II	**19 s, 1 d**	

Healer versus Investigator

The Fundamental Conflict

Healer versus Investigator: The Fundamental Conflict

A dilemma confronts physician-investigators… As physicians they are dedicated to caring for their patients… As investigators they are dedicated to caring for their research… These two commitments conflict whenever an individual physician/investigator comes face to face with an individual patient/subject.

Jay Katz, 1993

Should patients be warned?

"Researchers must give patients stark, bold, and dramatic signs that research is different from clinical care… instead of the white coats associated with medical care, investigators could wear red ones…"

Dresser R. Soc Philos Policy 2002; 19:271

Should patients be warned?

"This morning I was your doctor and you were my patient, but this afternoon I am going to be giving you an experimental medication, and then I am no longer your doctor, but an investigator, and you are my subject. During this time you need to know that I will place the pursuit of scientific knowledge above your interests, and will no longer be providing you with individualized care."

Truog RD, Int Care Med 2004, In Press

Possible Responses to this "Fundamental Conflict"

- "Different Hats"
  - Require that the clinician and the investigator never be the same individual
  - Difficult to do practically, and not always in the patient's best interest
- "Randomize the first patient"
  - Phase I and II trials, which precede RCTs, often provide strong evidence for effectiveness

Possible Responses to this "Fundamental Conflict"

- Personal Equipoise
  - Requires that the investigator be personally unbiased between the treatment arms, "perfectly balanced on the edge of the sword"
  - Researchers usually "believe in" the treatments they study
- Clinical Equipoise
  - Requires uncertainty within the medical profession as a whole
  - Does not require the individual investigator to be in a state of equipoise

Clinical Equipoise: Unresolved Issues

- "Clinical Equipoise" is not "Patient Equipoise"
  - Patients care about a more diverse range of outcome variables than clinicians
- When does clinical equipoise dissolve?
  - The arbitrary cutoff of $p < .05$
- When should the data be analyzed?
  - "Who wants to be the last patient enrolled in the control arm of a positive randomized controlled trial?"

Healer versus Investigator: The Fundamental Conflict

"Physicians traditionally act in the best interests of each patient under their care, and patients expect this of their physician. If this commitment to the patient is attenuated, even for so good a cause as benefits to future patients, the implicit assumptions of the doctor-patient relationship are violated. I have no doubt that we would lose more than we would gain by adopting such an approach."

Angell, NEJM, 1984

What's the solution?

- "What can be done when non-randomized designs are considered inadequate but randomization would be difficult…?"

- "Not all problems have solutions."

Marcia Angell, NEJM, 1984

Adaptive Randomization

Balancing Conflicting Obligations

Adaptive Randomization

- Definition: Deviating from “balanced” or 50/50 randomization, with more patients assigned to the therapy that is “leading” during the trial
- Betting on the horse in the lead, before we know how the race will end

Adaptive Randomization

- In the ECMO trial, 50/50 randomization until 4 deaths in one arm, then all patients got the more successful therapy
- Criticized from both directions
  - No patients should have been assigned to CMT
  - Not enough patients were assigned to CMT
- Perhaps this approach was a good balance

Adaptive Randomization: Advantages

- Attempts to resolve the conflict of healer versus investigator
- Attempts to minimize number of patients assigned to the less-successful therapy
- More consistent with current theories of continuous quality improvement

Adaptive Randomization: Disadvantages:

- Must be only one outcome of interest
- Outcomes must be apparent in a short period of time
- Requires more patients, thereby prolonging study

An Unconventional View: All Trials are Adaptive

- In a traditional trial we randomize 50/50 until we are about 95% sure that one treatment is better than another - then all patients receive the more effective treatment
- Proponents of adaptive designs are simply proposing that the transition toward the winning treatment should begin at an earlier stage, before we are 95% sure of the outcome

Adaptive Randomization

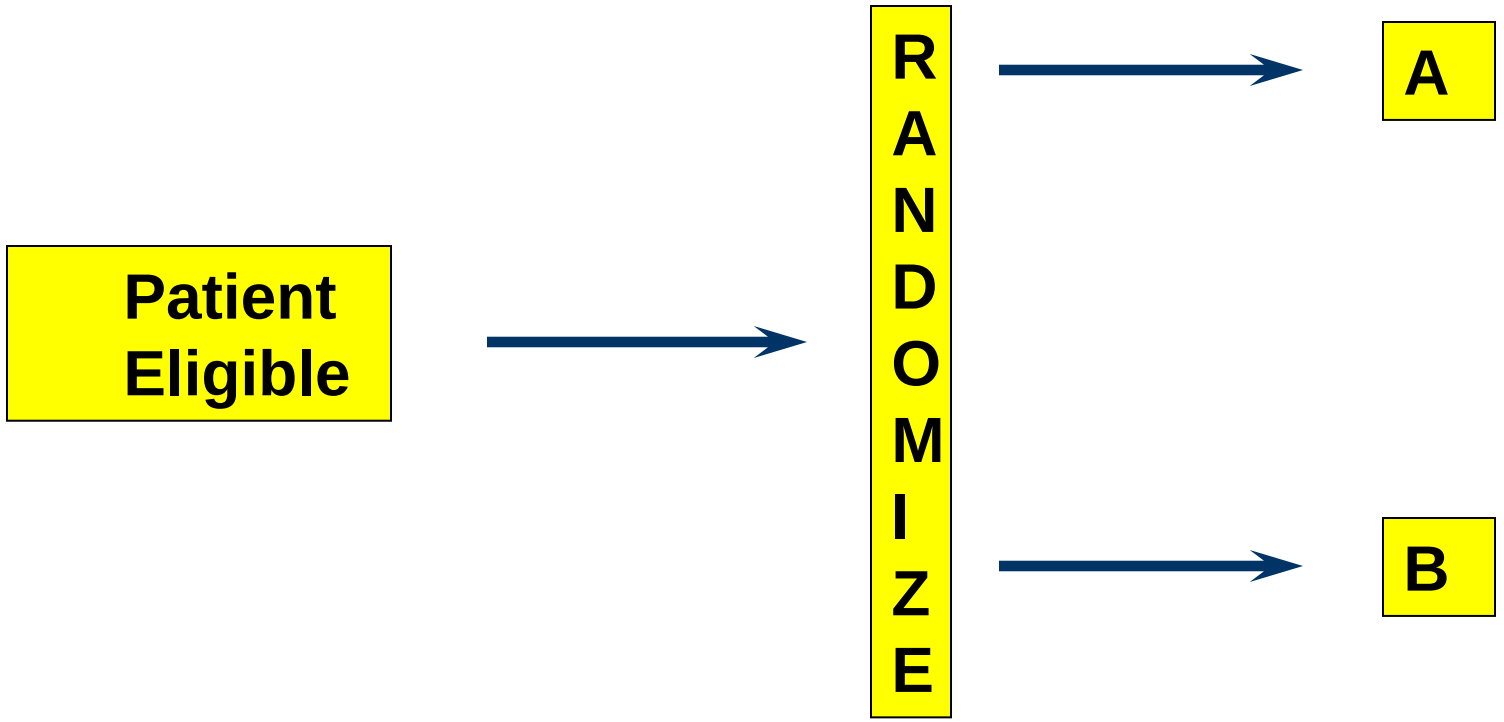
Adaptive methods should be used as a matter of course. It never pays to commit oneself to a protocol under which information available before the study or obtained during its course is ignored in the treatment of a patient.

Weinstein, NEJM, 1974

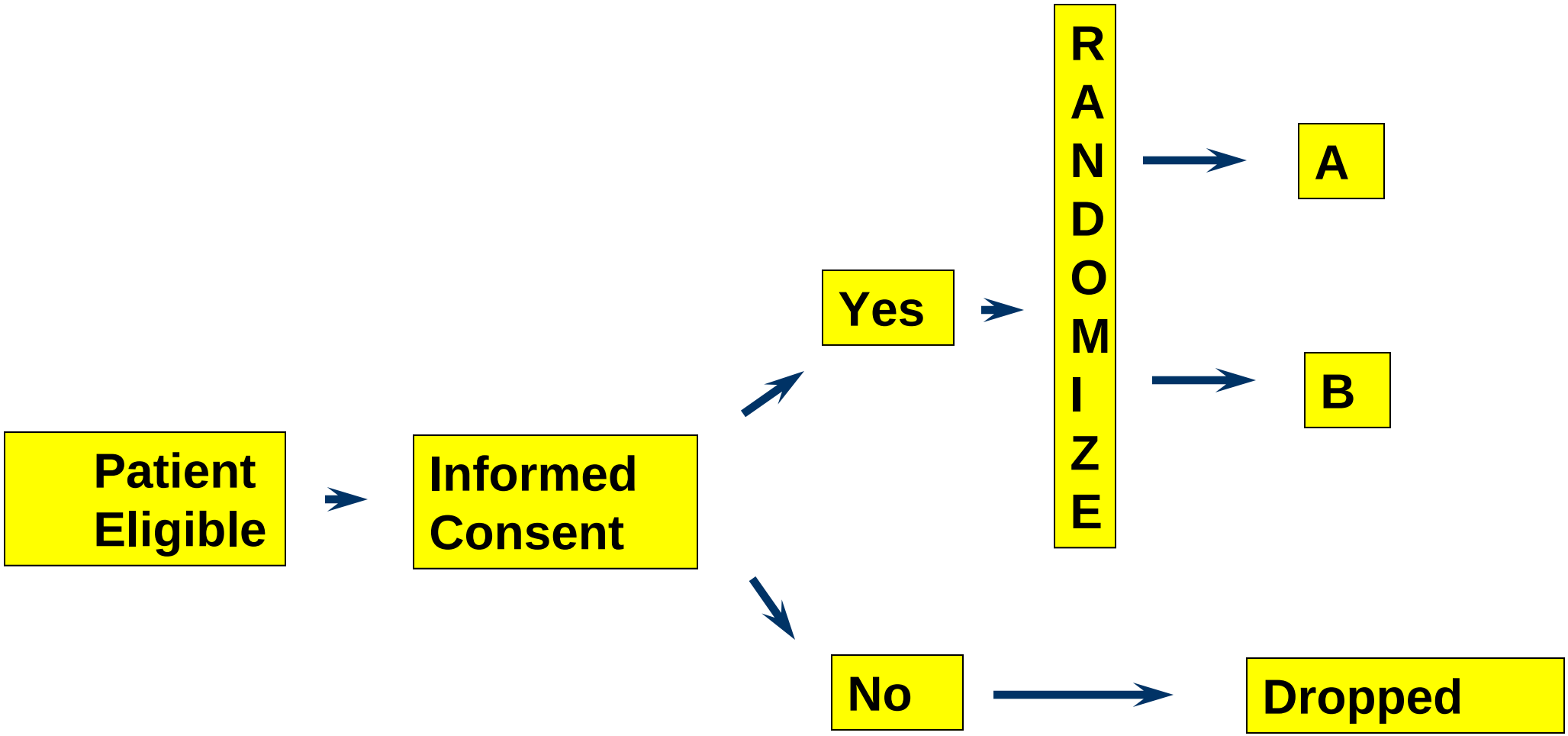
Randomized Consent

Easing the Psychological Burdens

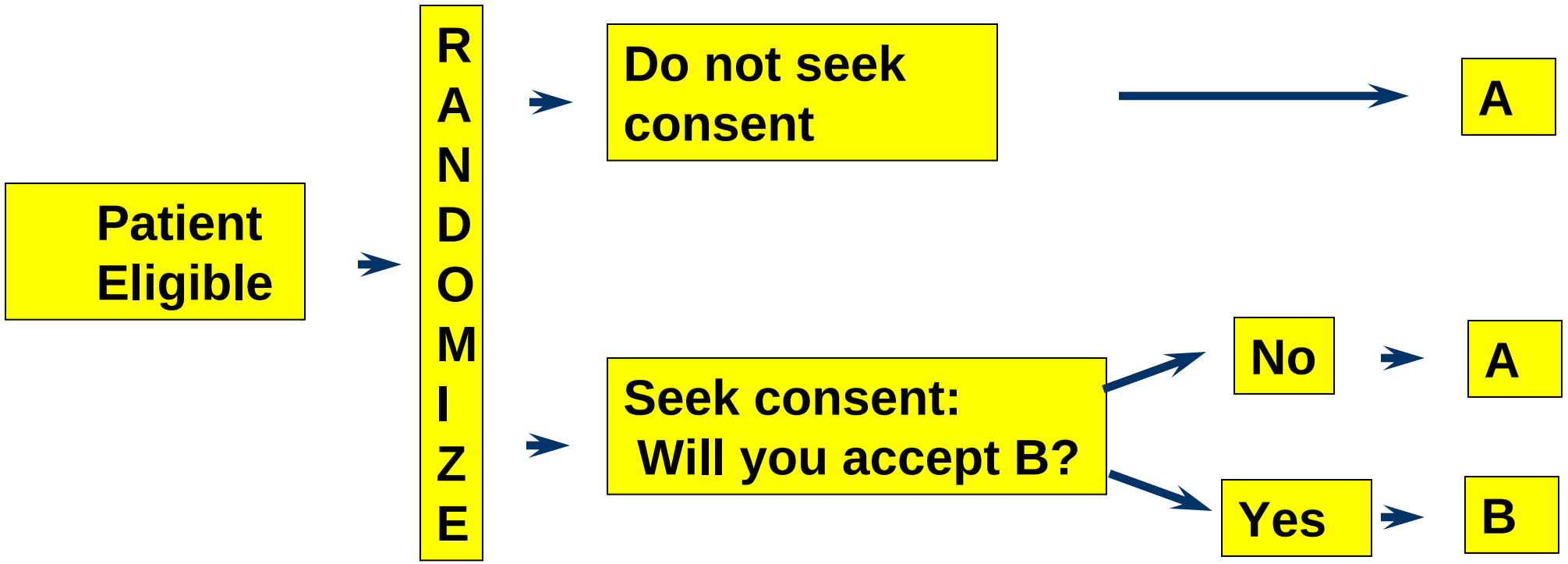
Conventional RCT, Without Informed Consent



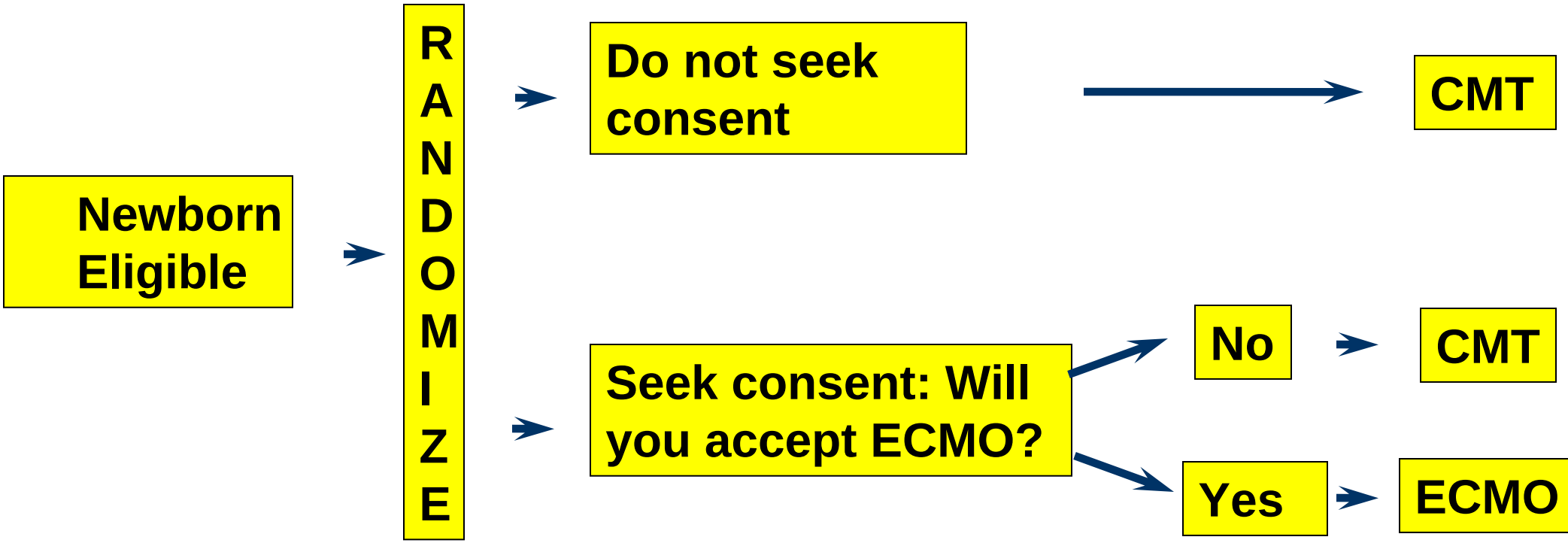
Conventional RCT, With Informed Consent



Randomized Consent



Randomized Consent



The ECMO Trial: Justifications for Randomized Consent

- Control patients were not really research subjects
- Parents of control patients were not really being offered a choice, so why subject them to stress?
- Pressure to cross-over from CMT to ECMO would have been unbearable

The Response to the ECMO Trial

The NIH Office for Protection from Research Risks (OPRR) reprimanded the hospital

The hospital IRB “made decisions that rightfully belonged to the parents. They really blew it.” **Charles McCarthy, Director of OPRR**

The doctors “were doing exactly what physicians did before we had a doctrine of informed consent - making decisions for parents.” **George Annas, Boston University**

Are RCTs the only way to learn?

Are RCTs the only way to learn?

- **“The brilliant success of the RCT has now become a form of intellectual tyranny”** ***Freireich***

- **“We should not proceed on the fallacious assumption that where there is no randomization, there is no truth.”** ***Royall***

Are RCTs the only way to learn?

"the claims for the RCT have been greatly, indeed preposterously overstated. The truth of the matter is that the RCT is one of many ways of generating information, of validating hypotheses. The proponents of the RCT, however, have elevated what is in theory a frequent (though by no means universal) advantage of degree into a gulf as sharp as that between the kosher and the non-kosher."

Fried

Approaches to Learning: Ascending Order of Confidence

- Anecdotal Case Reports
- Case Series without Controls
- Case Series with Literature Controls
- Case Series with Historical Controls
- Databases
- Case / Control Observational Studies
- Randomized Controlled Trials
- Meta-analyses

The New England Journal of Medicine

Special Articles

A COMPARISON OF OBSERVATIONAL STUDIES AND RANDOMIZED, CONTROLLED TRIALS

KJELL BENSON, B.A., AND ARTHUR J. HARTZ, M.D., PH.D.

Conclusions

We found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials. (N Engl J Med 2000;342:1878-86.)

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.

Conclusions

The results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic. (N Engl J Med 2000;342:1887-92.)

Are RCTs the only way to learn?

“The difference between the RCT and the observational, retrospective study is not the difference between good and bad science, truth or falsity, but a difference between varying degrees of confidence.” *Fried*

When should we think about alternatives to the RCT?

- When evaluating potentially life-saving therapies
  - subjects do not so much choose to enroll, but are chosen and then enrolled - relationship is fiduciary, not contractual
- Physicians are ambivalent
  - Survey of 415 physcians, most of whom experienced at research with potentially life-saving therapies
  - Only 35% would always strictly adhere to the protocol
  - If the patient deteriorated, many would seek to alter the protocol or seek compassionate use of the experimental treatment

Morris, Crit Care Med 2000, 28:1156

When should we think about alternatives to the RCT?

- When evaluating rapidly developing technologies
  - improvements in both experimental and control treatments may make the results of the RCT obsolete by the time it is published
- When RCTs are not the most efficient way to acquire knowledge
  - ARDSNet tidal volume study - $15 million
  - Confirmed a secular trend that was already occuring based on non-randomized data
  - Only one of multiple permutations of vent management

When should we think about alternatives to the RCT?

- When the non-randomized data are compelling...
- 1988: Database on 715 newborns treated with ECMO (Toomasian et al)
  - 81% survival
  - Statistically superior to any treatment with survival rate < 78.4%
- Was the Harvard Neonatal ECMO Trial Unnecessary?

The UK Neonatal ECMO Trial

- 1993-1995: 124 neonates randomized to ECMO vs CMT
- Trial stopped early by DSMB,
  - ECMO survival 60/93 = 65%
  - CMT survival 38/92 = 41%, $p<0.0005$

Conclusions

- The conflict between clinician and investigator is profound and can never be entirely eliminated
- Adaptive randomization is one way to balance the competing obligations
- Randomized consent reduces the psychological burdens of the investigators, but is probably ethically unacceptable

Conclusions

- RCTs are usually the best approach for evaluating new therapies
- Alternatives to RCTs should be considered:
  - when therapies are potentially life-saving
  - when the technologies are developing rapidly
  - when RCTs are not the most efficient method
  - when non-randomized data are compelling
- Investigators, journal editors, and granting agencies will have to reconsider their blind insistence upon RCTs for this to occur

Conclusions

"The use of statistics in medical research has been compared to a religion: it has its high priests (statisticians), supplicants (journal editors and researchers), and orthodoxy (for example, p<.05 is "significant")"

Benjamin Freedman